Public Assessment Report

Mutual Recognition Procedure

Clarithromycin 250mg Film-Coated Tablets
Clarithromycin 500mg Film-Coated Tablets

UK/H/0798/01-02
UK licence no: PL 00289/0457-8

Approved Prescription Services Limited

Clarithromycin 250mg Film-Coated Tablets
Clarithromycin 500mg Film-Coated Tablets

LAY SUMMARY

Austria, Belgium, Czech Republic, Finland, Germany, Hungary, Italy, Lithuania, Norway, Poland, Portugal, Slovak Republic and Sweden today granted Approved Prescription Services Limited Marketing Authorisations (licences) for the medicinal products Clarithromycin 250mg Film-Coated Tablets (PL 00289/0457) and Clarithromycin 500mg Film-Coated Tablets (PL 00289/0458). These are prescription only medicines (POM) for the treatment of acute and chronic bacterial infections, when caused by clarithromycin-susceptible bacteria.

Clarithromycin Film-Coated Tablets contain the active ingredient clarithromycin, which belongs to a group of drugs called macrolide antibiotics.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Clarithromycin 250mg and 500mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Clarithromycin 250mg Film-Coated Tablets Clarithromycin 500mg Film-Coated Tablets
Type of Application	Generic, Article 10.1(a)(iii), first paragraph
Active Substance	Clarithromycin
Form	Film-Coated Tablets
Strength	250mg and 500mg Film-Coated Tablets
MA Holder	Approved Prescription Services Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG
RMS	UK
CMS	Austria, Belgium, Czech Republic, Finland, Germany, Hungary, Italy, Lithuania, Norway, Poland, Portugal, Slovak Republic and Sweden
Procedure Number	UK/H/0798/01-02
Timetable	Day 90 – 16th November 2005

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
[Trade name of the product]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 250 mg clarithromycin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Yellow, film-coated oval shaped tablet, debossed with "93" on one side and "7157" on the other.

Clinical Particulars

4.1 Therapeutic Indications
Clarithromycin is indicated for the treatment of acute and chronic bacterial infections, when caused by clarithromycin-susceptible bacteria.

- Infections of the upper respiratory tract such as pharyngitis and sinusitis.
- Infections of the lower respiratory tract, such as acute exacerbation of chronic bronchitis, and community-acquired pneumonia.
- Skin and soft tissue infections of mild to moderate severity.

In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer-healing agent for the eradication of *H. pylori* in patients with *H. pylori*-associated ulcers. See section 4.2.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration
The dosage of clarithromycin depends on the clinical condition of the patient and has to be defined in any case by the physician.

250 and 500 mg tablets are available.

Adults and adolescents
The usual dose is 250 mg twice daily.
In severe infections, the dose may be increased to 500 mg twice daily.

In respiratory infections, owing to the high level of resistance of some pathogenic microorganisms (e.g. *S. pneumoniae*), penicillin remains the antibiotic of first choice. Clarithromycin may be used in patients with known hypersensitivity to penicillin or when penicillin would be inappropriate for other reasons.

Children
Clarithromycin tablets are not suitable for children under 12 years of age weighing less than 30 kg. Other pharmaceutical forms are more adapted for these patients.

Elderly
As for adults.

Eradication of *H. pylori* in adults
In patients with peptic ulcers due to *H. pylori* infection, clarithromycin can be administered in a dose of 500 mg twice daily in combination with other appropriate antimicrobe treatment and proton-pump inhibitors.

Renal impairment
Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance <30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections. The duration of treatment should not exceed 14 days in these patients.

Duration of therapy
The duration of therapy with clarithromycin depends on the clinical condition of the patient and in any case shall be determined by the physician.
- The usual duration of treatment is 7 to 14 days.
- Therapy should be continued for at least 2 days after symptoms have subsided.
- In infections caused by *Streptococcus pyogenes* (group A beta-haemolytic streptococci), the duration should be at least 10 days.

Combination therapy for the eradication of *H. pylori* infection, e.g. clarithromycin 500 mg (two 250 mg tablets or one 500 mg tablet) twice daily in combination with amoxicillin 1,000 mg twice daily and omeprazole 20 mg twice daily, should be continued for 7 days.

Method of administration
Clarithromycin may be given without regard to food intake (see section 5.2).

4.3 Contra-indications
- Hypersensitivity to the active substance clarithromycin, to other macrolides, or to any of the excipients.
- Concomitant administration with ergot derivatives (see section 4.5).
- Concomitant administration with cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides (see section 4.5).
- Hypokalaemia (risk of prolongation of QT-time).

4.4 Special Warnings and Special Precautions for Use
Clarithromycin is mainly excreted by the liver. Therefore, caution should be taken in administering clarithromycin to patients with impaired hepatic function or those concomitantly receiving potentially hepatotoxic products.

As with other antibiotics when renal function is poor, dosage of clarithromycin should be suitably reduced depending on the degree of the impairment (see section 4.2). In elderly patients, the possibility of renal impairment should be considered.

Clarithromycin therapy for *H. pylori* may select for substance-resistant organisms.

Patients who are hypersensitive to lincomycin or clindamycin may also be hypersensitive to clarithromycin. Therefore, caution is required when prescribing clarithromycin for such patients.

Prolonged or repeated use of clarithromycin may result in superinfections with insusceptible organisms. In case of superinfection, clarithromycin therapy should be stopped.

Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhoea during or after therapy with clarithromycin.

As known for other macrolides, clarithromycin may cause exacerbation or aggravation of myasthenia gravis and should therefore be used with caution in patients with myasthenia gravis.

Due to a risk of increased QT-interval, clarithromycin should be used with caution in patients with a coronary vessel disease, a history of ventricular arrhythmia, severe cardiac insufficiency, non-compensated hypokalemia and/or hypomagnesemia, bradycardia (<50 bpm), or when co-administered

with other medicinal products with a QT-prolonging effect. Clarithromycin should not be used in patients with congenital or documented acquired QT prolongation (see section 4.5).

Clarithromycin should be used with caution whenever indicated for use in patients receiving treatment with an inducer of CYP3A4 (see section 4.5).

Clarithromycin is an inhibitor of CYP3A4, and concomitant use with other medicinal products that are metabolised to a large extent by this enzyme should be restricted to situations where it is clearly indicated (see section 4.5).

Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products (see section 4.5).

This medicinal product contains tartrazine and may cause allergic reactions.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Contraindicated combinations

Concomitant administration of clarithromycin and terfenadine, cisapride, pimozide and ergot alkaloids is contraindicated.

The effect of other medicinal products on clarithromycin tablets

Clarithromycin is metabolised by the enzyme CYP3A4. Hence, strong inhibitors of this enzyme may inhibit the metabolism of clarithromycin, resulting in increased plasma concentrations of clarithromycin.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with antacids or ranitidine. No adjustment to the dosage is necessary.

Ritonavir (200 mg tid) has been shown to inhibit the metabolism of clarithromycin (500 mg bid), with an increase in C_{max}, C_{min} and AUC of 31, 182 and 77%, respectively, when co-administered with ritonavir. Formation of the active 14-OH-hydroxy metabolite was almost completely inhibited. A general dose reduction is probably not required in patients with normal renal function, but the daily dose of clarithromycin should not exceed 1 g. Dose reduction should be considered in patients with renal impairment. For patients with a creatinine clearance of 30 to 60 ml/min, the clarithromycin dose should be reduced with 50%, and at a creatinine clearance of <30 ml/min, the dose should be reduced with 75%.

Products that are inducers of CYP3A4 (eg rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. When clarithromycin is clearly indicated it might be necessary to increase the dose of clarithromycin and monitor its efficacy and safety carefully. Furthermore monitoring the plasma levels of the CYP3A4 inducer might be necessary because the latter could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase and decrease, respectively, in serum levels, followed by an increased risk of uveitis.

The effect of clarithromycin on other medicinal products

Clarithromycin is an inhibitor of the metabolising enzyme CYP3A4 and the transport protein P-glycoprotein. The degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, clarithromycin should not be used during treatment with other medicinal products that are substrates for CYP3A4, unless plasma levels, therapeutic effect or adverse events of the CYP3A4 substrate can be closely monitored. A dose reduction may be necessary for medicinal products that are substrates for CYP3A4 if co-administered with clarithromycin. Alternatively, treatment with these products may be interrupted during clarithromycin treatment.

Medicinal products with a potential to prolong QT-interval

Clarithromycin has been reported to inhibit the metabolism of cisapride and terfenadine, with a 2 to 3-fold increase in plasma levels reported for terfenadine. This has been associated with QT-prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar symptoms have been described for patients treated with pimozide when combined with

clarithromycin. Concomitant administration of clarithromycin and terfenadine, cisapride of pimozide is contraindicated (see section 4.3).

Cases with torsades de pointes has been reported in patients where clarithromycin has been co-administered with quinidine or disopyramide. These combinations should therefore be avoided, or plasma levels of quinidine or disopyramide closely monitored to allow dose adjustment. Caution is warranted when clarithromycin is administered to patients treated taking other medicinal products with the potential to prolong QT (see section 4.4).

HMG-CoA reductase inhibitors
Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products. Rhabdomyolysis in association with increased plasma concentrations have in rare cases been reported in patients treated with clarithromycin and simvastatin or lovastatin. Clarithromycin may produce a similar interaction with atorvastatin and a lesser interaction with either cerivastatin. When treatment with clarithromycin is indicated in patients receiving treatment with either simvastatin or lovastatin or atorvastatin or cerivastatin patients should be monitored for signs and symptoms of myopathy.

Ergot vasoconstrictors (eg dihydroergotamine, ergotamine)
Cases of ergotism due to increased plasma levels of ergot alkaloids have been reported when these products have been co-administered with macrolides. The combination is contraindicated (see section 4.3).

Benzodiazepines
When midazolam was co-administered with clarithromycin tablets (250 mg bid), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely mohnitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A4, especially triazolam but also alprazolam. For benzodiazepines which are not metabolised by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with clarithromycin is unlikely.

Cyclosporin, tacrolimus and sirolimus
Concomitant use of oral clarithromycin and cyclosporin or tacrolimus have results in more than a 2-fold increase of the C_{min} levels of both cyclosporin and tacrolimus. Similar effects are also expected for sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, cyclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses decreased as necessary. When clarithromycin is discontinued in these patients, close monitoring of plasma levels of cyclosporin, tacrolimus or sirolimus is again necessary to guide dose adjustment.

Digoxin
The concentration of digoxin may be increased when co-administered with clarithromycin. Monitoring of plasma levels of digoxin should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

Theophylline
The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity.

Warfarin
The use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

Zidovudine
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of clarithromycin and zidovudine by 1-2 hours. No such reaction has been reported in children.

4.6 Pregnancy and Lactation

Pregnancy

Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects, or of adverse effects or on the health of and neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available. Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should only be given to pregnant women after a careful benefit/risk assessment.

Lactation

Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on Ability to Drive and Use Machines

There are no data available on the effect of clarithromycin on the ability to drive or use machines. When performing these activities the possible occurrence of the adverse reactions dizziness, vertigo, confusion and disorientation should be taken into account.

4.8 Undesirable Effects

The most frequently reported undesirable effects in adults taking clarithromycin tablets were diarrhoea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%) and headache (2%).

In this section undesirable effects are defined as follows:
Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000).

Infections and infestations
Common: Oral monilia
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.

Blood and the lymphatic system disorders
Uncommon: Decreased leucocyte levels
Very rare: Thrombocytopenia

Immune system disorders
Uncommon: Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis

Psychiatric disorders
Very rare: Anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, bad dreams and confusion

Nervous system disorders
Common: Headache, smell alteration
Very rare: Dizziness, vertigo, paraesthesia, convulsions

Ear and labyrinth disorders
Rare: Tinnitus
Very rare: Reversible hearing loss

Cardiac disorders
Very rare: QT prolongation, ventricular tachycardia and Torsades de Pointes.

Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discoloration, and taste perversion, i.e. metallic or bitter taste.
Very rare: Pancreatitis. Pseudomembranous colitis has been reported very rarely with clarithromycin, and may range in severity from mild to life threatening.

Hepato-biliary disorders
Uncommon: Hepatic dysfunction, which is usually transient and reversible, hepatitis and cholestasis with or without jaundice.
Very rare: Fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic medicinal products.

Skin and subcutaneous tissue disorders
Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, myalgia.

Renal and urinary disorders
Very rare: Interstitial nephritis, renal failure.

Investigations
Common: Elevated BUN
Uncommon: Prolongation of prothrombin time, elevated serum creatinine, altered liver function tests (increased transaminase levels).
Very rare: Hypoglycaemia has been observed especially after concomitant administration with antidiabetic medicinal products and insulin

4.9. Overdose

Symptoms of intoxication:
Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokaliaemia and hypoxaemia.

Therapy of intoxication:
There is no specific antidote on overdose. Serum levels of clarithromycin can not be reduced by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At the first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

5 Pharmacological Properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Macrolides
ATC code: J01F A09

Mechanism of action
Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Mechanisms of resistance
Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exist constitutively. Macrolide-resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramin B based on methylation of the ribosomal binding site. Clarithromycin ranks among the strong inducers of this

enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes.

A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae* are resistant to macrolides such as clarithromycin.

Breakpoints
According to the NCCLS (US National Committee on Clinical Laboratory Standards) in 2003 the following breakpoints have been defined for clarithromycin:
- *Staphylococcus* spp.: ≤2 µg/ml susceptible, ≥8 µg/ml resistant
- *Haemophilus* spp.: ≤8 µg/ml susceptible
- *Streptococcus* spp. including *S. pneumoniae*: ≤0.25 µg/ml susceptible, ≥1 µg/ml resistant

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species (ie resistance < 10 % in all EU Member States)
Aerobic, Gram-positive microorganisms
Streptococcus group A
Streptococcus group B
Streptococcus group C,F,G
Aerobic, Gram-negative microorganisms
Moraxella catarrhalis
Pasteurella multocida
Legionella spp.
Anaerobic microorganisms
Bacteroides spp.
Peptococcus/Peptostreptococcus spp.
Clostridium spp., other than *C. difficile*
Fusobacterium spp.
Other microorganisms
Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydia pneumoniae
Species for which acquired resistance may be a problem (ie resistance ≥ 10 % in at least 1 EU Member State)
Aerobic, Gram-positive microorganisms
Staphylococcus aureus, methicillin-susceptible
*Streptococcus pneumoniae**
Aerobic, Gram-negative microorganisms
Haemophilus influenzae
Helicobacter pylori
Inherently resistant microorganisms
Aerobic, Gram-positive microorganisms
Enterococcus spp.
Staphylococcus aureus, methicillin-resistant or erythromycin-resistant
Other microorganisms
Mycobacterium tuberculosis

*****Comments regarding resistance see "Mechanisms of resistance"

5.2. Pharmacokinetic Properties

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract - primarily in the jejunum - but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250 mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to

food. Due to its chemical structure (6-O-methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1-2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml.

After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:
Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400 l. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating substance levels. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C 14.

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. The elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.

After oral administration of radioactive clarithromycin 70-80% of the radioactivity was found in the faeces. Approximately 20-30% of clarithromycin is collected as the unchanged active substance in the urine. This proportion is increased when the dose is increased. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased.

Total plasma clearance has been estimated to approximately 700 ml/min, with a renal clearance of approximately 170 ml/min.

Special populations:
Renal impairment: Reduced renal function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

5.3 Preclinical Safety Data

In 4-week studies in animals, the toxicity of clarithromycin was found to be related to the dose and duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure related to this toxicity are not known in detail, but toxic doses were clearly higher than the therapeutic doses recommended for humans.

No mutagenic effects were found in *in vitro* or *in vivo* studies with clarithromycin.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and x10 the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was noted in rat studies. However, cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/day. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Sodium starch glycolate
Microcrystalline cellulose
Povidone (PVP K-30)
Magnesium hydroxide
Croscarmellose sodium

Colloidal anhydrous silica
Stearic acid
Magnesium stearate

Film-coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Tartrazine lake (E102)
Allura Red AC Lake (E129)
Indigo Carmine Lake (E132)
Vanillin

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
2 years

6.4 Special Precautions for Storage
Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and Contents of Container
Available in blister packs of transparent or white opaque PVC or PVC/PVdC lidded with aluminium foil for 10, 12, 14, 14 calendar pack, 20 & 120 (10x12) as hospital pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

Administrative Data

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
[Trade name of the product]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 500 mg clarithromycin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Light yellow, film-coated oval shaped tablet, debossed with "93" on one side and "7158" on the other.

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4.1 Therapeutic Indications
Clarithromycin is indicated for the treatment of acute and chronic bacterial infections, when caused by clarithromycin-susceptible bacteria.

- Infections of the upper respiratory tract such as pharyngitis and sinusitis.
- Infections of the lower respiratory tract, such as acute exacerbation of chronic bronchitis, and community-acquired pneumonia.
- Skin and soft tissue infections of mild to moderate severity.

In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer-healing agent for the eradication of *H. pylori* in patients with *H. pylori associated* ulcers. See section 4.2.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration
The dosage of clarithromycin depends on the clinical condition of the patient and has to be defined in any case by the physician.

250 and 500 mg tablets are available.

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In severe infections, the dose may be increased to 500 mg twice daily.

In respiratory infections, owing to the high level of resistance of some pathogenic microorganisms (e.g. *S. pneumoniae*), penicillin remains the antibiotic of first choice. Clarithromycin may be used in patients with known hypersensitivity to penicillin or when penicillin would be inappropriate for other reasons.

Children
Clarithromycin tablets are not suitable for children under 12 years of age weighing less than 30 kg. Other pharmaceutical forms are more adapted for these patients.

Elderly
As for adults.

Eradication of *H. pylori* in ddults
In patients with peptic ulcers due to *H. pylori* infection, clarithromycin can be administered in a dose of 500 mg twice daily in combination with other appropriate antimicrobe treatment and proton-pump inhibitors.

Renal impairment
Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance <30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections. The duration of treatment should not exceed 14 days in these patients.

Duration of therapy

The duration of therapy with clarithromycin depends on the clinical condition of the patient and in any case shall be determined by the physician.

- The usual duration of treatment is 7 to 14 days.
- Therapy should be continued for at least 2 days after symptoms have subsided.
- In infections caused by *Streptococcus pyogenes* (group A beta-haemolytic streptococci), the duration should be at least 10 days.

Combination therapy for the eradication of *H. pylori* infection, e.g. clarithromycin 500 mg (two 250 mg tablets or one 500 mg tablet) twice daily in combination with amoxicillin 1,000 mg twice daily and omeprazole 20 mg twice daily, should be continued for 7 days.

Method of administration

Clarithromycin may be given without regard to food intake (see section 5.2).

4.3 Contra-indications

- Hypersensitivity to the active substance clarithromycin, to other macrolides, or to any of the excipients.
- Concomitant administration with ergot derivatives (see section 4.5).
- Concomitant administration with cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides (see section 4.5).
- Hypokalaemia (risk of prolongation of QT-time).

4.4 Special Warnings and Special Precautions for Use

Clarithromycin is mainly excreted by the liver. Therefore, caution should be taken in administering clarithromycin to patients with impaired hepatic function or those concomitantly receiving potentially hepatotoxic products.

As with other antibiotics when renal function is poor, dosage of clarithromycin should be suitably reduced depending on the degree of the impairment (see section 4.2). In elderly patients, the possibility of renal impairment should be considered.

Clarithromycin therapy for *H. pylori* may select for substance-resistant organisms.

Patients who are hypersensitive to lincomycin or clindamycin may also be hypersensitive to clarithromycin. Therefore, caution is required when prescribing clarithromycin for such patients.

Prolonged or repeated use of clarithromycin may result in superinfections with insusceptible organisms. In case of superinfection, clarithromycin therapy should be stopped.

Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhoea during or after therapy with clarithromycin.

As known for other macrolides, clarithromycin may cause exacerbation or aggravation of myasthenia gravis and should therefore be used with caution in patients with myasthenia gravis.

Due to a risk of increased QT-interval, clarithromycin should be used with caution in patients with a coronary vessel disease, a history of ventricular arrhythmia, severe cardiac insufficiency, non-compensated hypokalemia and/or hypomagnesemia, bradycardia (<50 bpm), or when co-administered with other medicinal products with a QT-prolonging effect. Clarithromycin should not be used in patients with congenital or documented acquired QT prolongation (see section 4.5).

Clarithromycin should be used with caution whenever indicated for use in patients receiving treatment with an inducer of CYP3A4 (see section 4.5).

Clarithromycin is an inhibitor of CYP3A4, and concomitant use with other medicinal products that are metabolised to a large extent by this enzyme should be restricted to situations where it is clearly indicated (see section 4.5).

Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products (see section 4.5).

This medicinal product contains tartrazine and may cause allergic reactions.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Contraindicated combinations

Concomitant administration of clarithromycin and terfenadine, cisapride, pimozide and ergot alkaloids is contraindicated.

The effect of other medicinal products on clarithromycin tablets

Clarithromycin is metabolised by the enzyme CYP3A4. Hence, strong inhibitors of this enzyme may inhibit the metabolism of clarithromycin, resulting in increased plasma concentrations of clarithromycin.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with antacids or ranitidine. No adjustment to the dosage is necessary.

Ritonavir (200 mg tid) has been shown to inhibit the metabolism of clarithromycin (500 mg bid), with an increase in C_{max}, C_{min} and AUC of 31, 182 and 77%, respectively, when co-administered with ritonavir. Formation of the active 14-OH-hydroxy metabolite was almost completely inhibited. A general dose reduction is probably not required in patients with normal renal function, but the daily dose of clarithromycin should not exceed 1 g. Dose reduction should be considered in patients with renal impairment. For patients with a creatinine clearance of 30 to 60 ml/min, the clarithromycin dose should be reduced with 50%, and at a creatinine clearance of <30 ml/min, the dose should be reduced with 75%.

Products that are inducers of CYP3A4 (eg rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. When clarithromycin is clearly indicated it might be necessary to increase the dose of clarithromycin and monitor its efficacy and safety carefully. Furthermore monitoring the plasma levels of the CYP3A4 inducer might be necessary because the latter could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase and decrease, respectively, in serum levels, followed by an increased risk of uveitis.

The effect of clarithromycin on other medicinal products

Clarithromycin is an inhibitor of the metabolising enzyme CYP3A4 and the transport protein P-glycoprotein. The degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, clarithromycin should not be used during treatment with other medicinal products that are substrates for CYP3A4, unless plasma levels, therapeutic effect or adverse events of the CYP3A4 substrate can be closely monitored. A dose reduction may be necessary for medicinal products that are substrates for CYP3A4 if co-administered with clarithromycin. Alternatively, treatment with these products may be interrupted during clarithromycin treatment.

Medicinal products with a potential to prolong QT-interval

Clarithromycin has been reported to inhibit the metabolism of cisapride and terfenadine, with a 2 to 3-fold increase in plasma levels reported for terfenadine. This has been associated with QT-prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar symptoms have been described for patients treated with pimozide when combined with clarithromycin. Concomitant administration of clarithromycin and terfenadine, cisapride of pimozide is contraindicated (see section 4.3).

Cases with torsades de pointes has been reported in patients where clarithromycin has been co-administered with quinidine or disopyramide. These combinations should therefore be avoided, or plasma levels of quinidine or disopyramide closely monitored to allow dose adjustment. Caution is warranted when clarithromycin is administered to patients treated taking other medicinal products with the potential to prolong QT (see section 4.4).

HMG-CoA reductase inhibitors
Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products. Rhabdomyolysis in association with increased plasma concentrations have in rare cases been reported in patients treated with clarithromycin and simvastatin or lovastatin. Clarithromycin may produce a similar interaction with atorvastatin and a lesser interaction with either cerivastatin. When treatment with clarithromycin is indicated in patients receiving treatment with either simvastatin or lovastatin or atorvastatin or cerivastatin patients should be monitored for signs and symptoms of myopathy.

Ergot vasoconstrictors (eg dihydroergotamine, ergotamine)
Cases of ergotism due to increased plasma levels of ergot alkaloids have been reported when these products have been co-administered with macrolides. The combination is contraindicated (see section 4.3).

Benzodiazepines
When midazolam was co-administered with clarithromycin tablets (250 mg bid), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely mohnitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A4, especially triazolam but also alprazolam. For benzodiazepines which are not metabolised by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with clarithromycin is unlikely.

Cyclosporin, tacrolimus and sirolimus
Concomitant use of oral clarithromycin and cyclosporin or tacrolimus have results in more than a 2-fold increase of the C_{min} levels of both cyclosporin and tacrolimus. Similar effects are also expected for sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, cyclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses decreased as necessary. When clarithromycin is discontinued in these patients, close monitoring of plasma levels of cyclosporin, tacrolimus or sirolimus is again necessary to guide dose adjustment.

Digoxin
The concentration of digoxin may be increased when co-administered with clarithromycin. Monitoring of plasma levels of digoxin should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

Theophylline
The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity.

Warfarin
The use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

Zidovudine
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of clarithromycin and zidovudine by 1-2 hours. No such reaction has been reported in children.

4.6 Pregnancy and Lactation

Pregnancy
Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects, or of adverse effects or on the health of and neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available. Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should only be given to pregnant women after a careful benefit/risk assessment.

Lactation
Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to

be discontinued. The possibility of sensitisation should be borne in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on Ability to Drive and Use Machines

There are no data available on the effect of clarithromycin on the ability to drive or use machines. When performing these activities the possible occurrence of the adverse reactions dizziness, vertigo, confusion and disorientation should be taken into account.

4.8 Undesirable Effects

The most frequently reported undesirable effects in adults taking clarithromycin tablets were diarrhoea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%) and headache (2%).

In this section undesirable effects are defined as follows:
Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000).

Infections and infestations
Common: Oral monilia
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.

Blood and the lymphatic system disorders
Uncommon: Decreased leucocyte levels
Very rare: Thrombocytopenia

Immune system disorders
Uncommon: Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis

Psychiatric disorders
Very rare: Anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, bad dreams and confusion

Nervous system disorders
Common: Headache, smell alteration
Very rare: Dizziness, vertigo, paraesthesia, convulsions

Ear and labyrinth disorders
Rare: Tinnitus
Very rare: Reversible hearing loss

Cardiac disorders
Very rare: QT prolongation, ventricular tachycardia and Torsades de Pointes.

Gastrointestinal disorders
Common: Nausea, diarrhoea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discoloration, and taste perversion, i.e. metallic or bitter taste.
Very rare: Pancreatitis. Pseudomembranous colitis has been reported very rarely with clarithromycin, and may range in severity from mild to life threatening.

Hepato-biliary disorders
Uncommon: Hepatic dysfunction, which is usually transient and reversible, hepatitis and cholestasis with or without jaundice.
Very rare: Fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic medicinal products.

Skin and subcutaneous tissue disorders
Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, myalgia.

Renal and urinary disorders
Very rare: Interstitial nephritis, renal failure.

Investigations
Common: Elevated BUN
Uncommon: Prolongation of prothrombin time, elevated serum creatinine, altered liver function tests (increased transaminase levels).
Very rare: Hypoglycaemia has been observed especially after concomitant administration with antidiabetic medicinal products and insulin

4.9 Overdose

Symptoms of intoxication:
Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokaliaemia and hypoxaemia.

Therapy of intoxication:
There is no specific antidote on overdose. Serum levels of clarithromycin can not be reduced by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At the first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

5 Pharmacological Properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Macrolides
ATC code J01F A09

Mechanism of action
Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Mechanisms of resistance
Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exist constitutively. Macrolide-resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramin B based on methylation of the ribosomal binding site. Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes.

A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae* are resistant to macrolides such as clarithromycin.

Breakpoints
According to the NCCLS (US National Committee on Clinical Laboratory Standards) in 2003 the following breakpoints have been defined for clarithromycin:
- *Staphylococcus* spp.: ≤2 µg/ml susceptible, ≥8 µg/ml resistant
- *Haemophilus* spp.: ≤8 µg/ml susceptible
- *Streptococcus* spp. including *S. pneumoniae*: ≤0.25 µg/ml susceptible, ≥1 µg/ml resistant

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species (ie resistance < 10 % in all EU Member States)
Aerobic, Gram-positive microorganisms
Streptococcus group A
Streptococcus group B
Streptococcus group C,F,G
Aerobic, Gram-negative microorganisms
Moraxella catarrhalis
Pasteurella multocida
Legionella spp.
Anaerobic microorganisms
Bacteroides spp.
Peptococcus/Peptostreptococcus spp.
Clostridium spp., other than *C. difficile*
Fusobacterium spp.
Other microorganisms
Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydia pneumoniae
Species for which acquired resistance may be a problem (ie resistance ≥ 10 % in at least 1 EU Member State)
Aerobic, Gram-positive microorganisms
Staphylococcus aureus, methicillin-susceptible
*Streptococcus pneumoniae**
Aerobic, Gram-negative microorganisms
Haemophilus influenzae
Helicobacter pylori
Inherently resistant microorganisms
Aerobic, Gram-positive microorganisms
Enterococcus spp.
Staphylococcus aureus, methicillin-resistant or erythromycin-resistant
Other microorganisms
Mycobacterium tuberculosis

*Comments regarding resistance see "Mechanisms of resistance"

5.1 Pharmacokinetic Properties

Absorption:

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract - primarily in the jejunum - but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250 mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1-2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml.

After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:

Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400 l. Clarithromycin provides concentrations in some tissues that are several times higher than

the circulating substance levels. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C 14.

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. The elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.

After oral administration of radioactive clarithromycin 70-80% of the radioactivity was found in the faeces. Approximately 20-30% of clarithromycin is collected as the unchanged active substance in the urine. This proportion is increased when the dose is increased. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased.

Total plasma clearance has been estimated to approximately 700 ml/min, with a renal clearance of approximately 170 ml/min.

Special populations:
Renal impairment: Reduced renal function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

5.3 Preclinical Safety Data

In 4-week studies in animals, the toxicity of clarithromycin was found to be related to the dose and duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure related to this toxicity are not known in detail, but toxic doses were clearly higher than the therapeutic doses recommended for humans.

No mutagenic effects were found in *in vitro* or *in vivo* studies with clarithromycin.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and x10 the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was noted in rat studies. However, cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/day. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Sodium starch glycolate
Microcrystalline cellulose
Povidone (PVP K-30)
Magnesium hydroxide
Croscarmellose sodium
Colloidal anhydrous silica
Stearic acid
Magnesium stearate
Film-coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Tartrazine lake (E102)
Allura Red AC Lake (E129)
Indigo Carmine Lake (E132)
Vanillin

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
2 years

6.4 Special Precautions for Storage
Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and Contents of Container
Available in blister packs of transparent or white opaque PVC or PVC/PVdC lidded with aluminium foil for 10, 14, 14 calendar pack & 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

Administrative Data

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

Module 3

Product Information Leaflet

APS®

PATIENT INFORMATION LEAFLET

CLARITHROMYCIN 250 & 500 mg FILM-COATED TABLETS

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

The name of your medicine is **Clarithromycin 250 mg or 500 mg Film-Coated Tablets**.

- The active ingredient is clarithromycin.
- Other ingredients are sodium starch glycolate, microcrystalline cellulose, povidone, magnesium hydroxide, croscarmellose sodium, anhydrous colloidal silica, stearic acid, magnesium stearate, hypromellose, titanium dioxide (E171), macrogol, tartrazine (E102), allura red (E129), indigo carmine (E132) and vanillin.

The Marketing Authorisation holder and company responsible for manufacture: Approved Prescription Services Limited, Eastbourne BN22 9AG England.

1. CLARITHROMYCIN; WHAT IT IS AND WHAT IT'S USED FOR

- Each tablet contains either 250 mg or 500 mg of clarithromycin.

Clarithromycin belongs to a group of drugs called macrolide antibiotics.

- The product is available in a pack size of 14 tablets.
- Your medicine can be used to treat a range of infections such as:
  - Chest infections e.g. bronchitis and pneumonia
  - Throat and sinus infections e.g. sinusitis and pharyngitis
  - Skin and tissue infections
  - *Helicobacter pylori* infection associated with duodenal ulcer.

2. BEFORE YOU TAKE CLARITHROMYCIN

Do not take Clarithromycin if you:

- Are sensitive to any of the ingredients in your medicine, or to any other macrolide antibiotic e.g. erythromycin
- Are taking ergotamine or dihydroergotamine (to treat migraines)
- Are taking terfenadine or astemizole (used to treat hay fever and other allergies)
- Are taking pimozide (used to treat mental disorders)
- Are taking cisapride (used to treat stomach problems).

Take special care with Clarithromycin if you have:

- Liver problems
- Kidney problems.

Be careful if you are taking any of the following:

- Coumarin anticoagulants used to thin your blood, e.g. warfarin
- Other macrolides e.g. erythromycin or azithromycin
- Medicines used to treat an abnormal heart beat, e.g. disopyramide or digoxin
- Medicines used to treat epilepsy, e.g. phenytoin or carbamazepine
- Theophylline, used to treat asthma
- Benzodiazepines used as sedatives, e.g. midazolam or triazolam
- Rifabutin, used to treat some infections
- Ciclosporin or tacrolimus, used following organ transplant
- Medicines used to lower cholesterol, e.g. simvastatin or lovastatin
- Ritonavir or zidovudine, used to treat HIV infected patients.

Clarithromycin does not interact with oral contraceptives.

Pregnancy and Breast-feeding:

- Consult your doctor first before taking Clarithromycin if you are pregnant or breast-feeding.

Important information about some of the ingredients of Clarithromycin

E102 can cause an allergic-type reaction, including asthma. This reaction is more common in those people who are allergic to aspirin.

3. HOW TO TAKE CLARITHROMYCIN

Your doctor has decided the dose which is suited to you. Always follow your doctor's instructions and those which are on the pharmacy label. If you do not understand these instructions, or you are in any doubt, ask your doctor or pharmacist.

The tablets should be swallowed with at least half a glass of water.

The usual dosage instructions are given below:

For chest infections, throat or sinus infections and skin and soft tissue infections:

Adults and children over 12 years old:

250 mg twice a day for 7 days. Your doctor may increase the dose to 500 mg twice a day in severe infections.

Patients with kidney problems:

If you have severe kidney problems your doctor may need to reduce your dose.

Patients with liver problems:

If you have liver problems your doctor may need to reduce your dose.

Children under 12 years old:
Not recommended.

For the treatment of *Helicobacter pylori* infection associated with duodenal ulcers:
Clarithromycin is taken in combination with other medicines to treat *Helicobacter pylori*.
The combinations include:

1. One 500 mg clarithromycin tablet taken twice a day with 1000 mg amoxycillin twice a day and 20 mg omeprazole once a day for 10 days.
2. One 500 mg clarithromycin tablet taken twice a day with 30 mg lansoprazole twice a day and 1000 mg amoxycillin twice a day for 7-14 days.
3. One 500 mg clarithromycin tablet taken twice a day with 30 mg lansoprazole twice a day and 400 mg metronidazole twice a day for 7 days.
4. One 500 mg clarithromycin tablet taken twice a day with 40 mg omeprazole once a day with either 1000 mg amoxycillin twice a day or 400 mg metronidazole twice a day for 7 days.
5. One 500 mg clarithromycin tablet taken three times a day for 14 days with 40 mg omeprazole once a day.

Your doctor will decide on the best treatment combination for you. The treatment combination may differ from those given above. If you are at all unsure as to which medicine to take and when to take the medicine you must speak to your doctor. Do not stop taking your medicine because you are feeling better. It is important that you complete your prescribed dose, otherwise the problem may come back.

If you take more Clarithromycin than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. An overdose is likely to cause vomiting and stomach pains. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Clarithromycin
If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clarithromycin can have side effects.
If the following happens, stop taking Clarithromycin and tell your doctor immediately or go to the casualty department at your nearest hospital:
An allergic reaction causing

- Difficulty in breathing and swelling of the lips, face and neck
- Skin rash, which may range in severity from itchy skin eruptions to serious blistering of the skin or ulceration of the lips, eyes, nose, mouth and genitals.

This is a serious but rare side effect. You may need urgent medical attention or hospitalisation.

Other possible side effects include:

- Stomach problems such as nausea, vomiting, indigestion, stomach pains, or diarrhoea
- Prolonged attacks of diarrhoea, which has blood or mucus in it (if this occurs you must consult your doctor immediately)
- Numbness or pins-and-needles
- Headache
- Joint pain and muscle pain
- Inflammation of the mouth or tongue, tongue discolouration, thrush in the mouth (causing soreness of the mouth sometimes accompanied by white spots)
- Change in sense of taste or smell, funny taste in your mouth
- Teeth discolouration (this can usually be corrected by professional cleaning).

The side effects given below are usually short lived and soon disappear:

- Dizziness, vertigo, disorientation
- Ringing in the ears
- Difficulty sleeping, bad dreams, hallucinations
- Confusion, change in the sense of reality and feeling panicky.

Rare side effects include:

- Low blood sugar levels or a 'hypo' in diabetic patients
- Hearing loss (usually reversible on withdrawal of treatment)
- Blood disorders which may be characterised by fever chills, sore throat, ulcers in your mouth
- Unusual bleeding or unexplained bruising
- Liver or gall bladder problems
- Jaundice - yellowing of the skin and the whites of the eyes
- Changes in blood test results
- Kidney problems
- Fits
- Pancreatitis - nausea, vomiting, abdominal pain and back pain
- Changes in heart beat/rhythm.

Tell your doctor if you notice any of the side effects listed above.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING CLARITHROMYCIN

Keep Clarithromycin out of the reach and sight of children. Do not store above 30°C. Keep the container in the outer carton. Do not transfer to another container. Do not use Clarithromycin after the expiry date shown on the outer packaging. Return all unused medicines to your pharmacist for safe disposal.

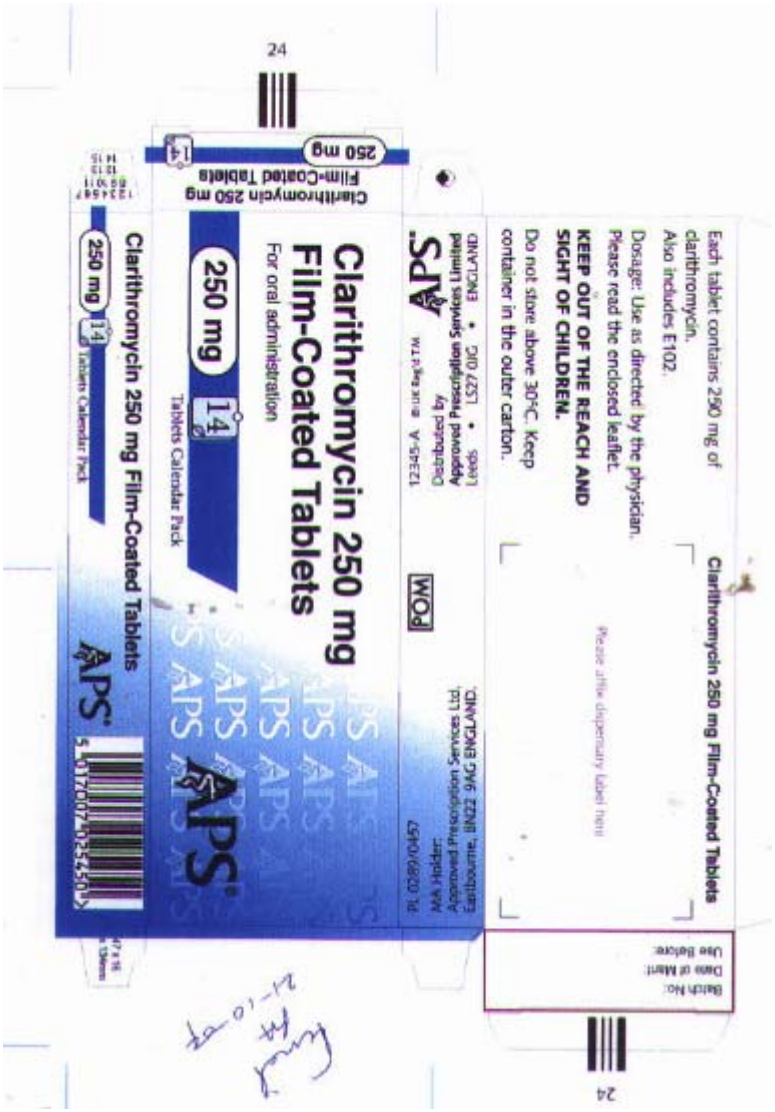
Revised: June 2003

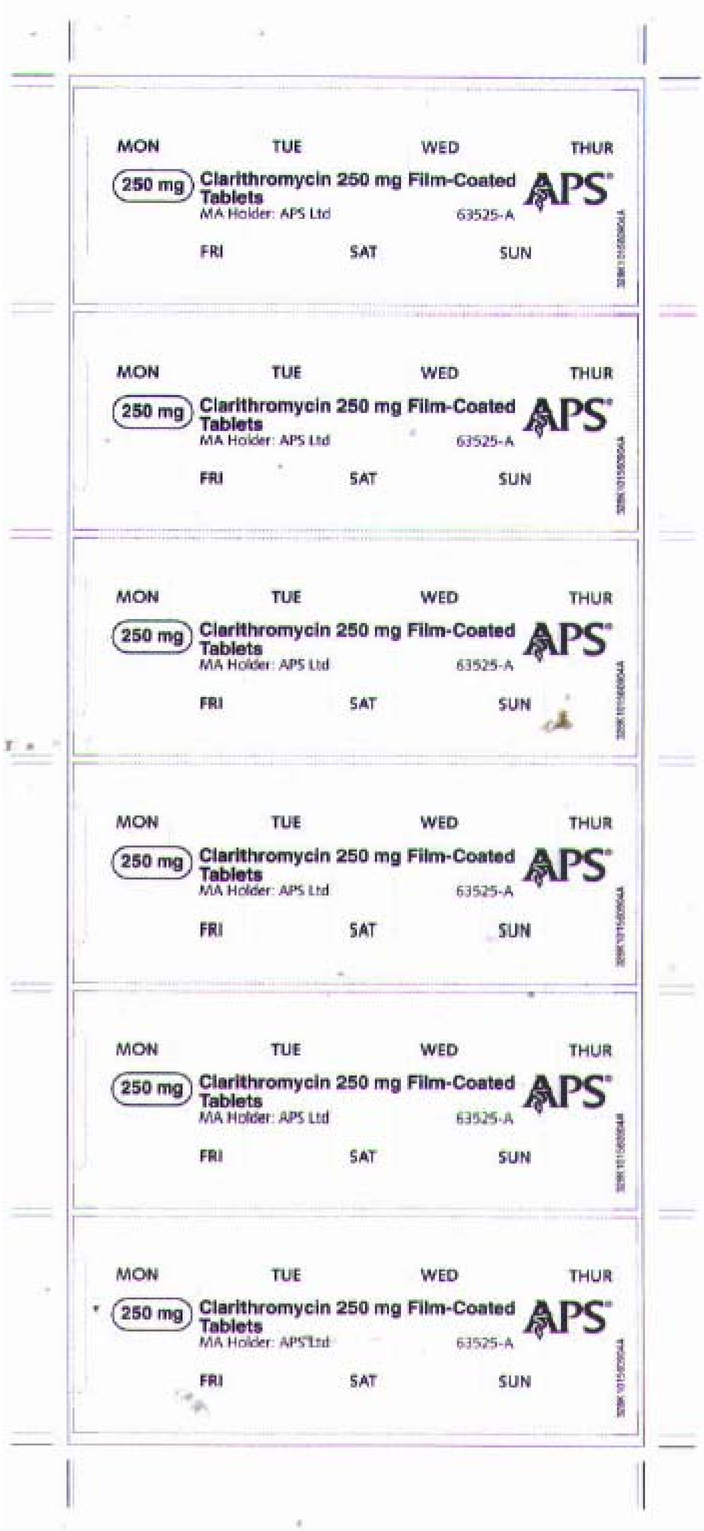
63513-A

Distributed by Approved Prescription Services Limited, Leeds LS27 0JG, England. 322K001590904A

Module 4

Labelling

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Clarithromycin 250 mg Film-Coated Tablets
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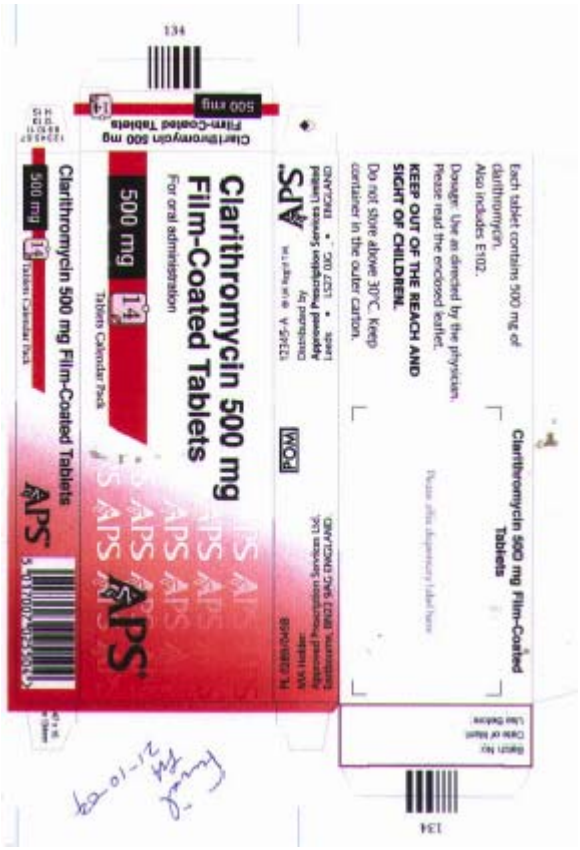
Clarithromycin 500 mg Film-Coated Tablets
Each tablet contains 500 mg of clarithromycin.
Also includes E102.
Dosage: Use as directed by the physician.
Please read the enclosed leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 30°C. Keep container in the outer carton.
Clarithromycin 500 mg Film-Coated Tablets
500 mg
14 Tablets Calendar Pack
APS
Clarithromycin 500 mg Film-Coated Tablets
For oral administration
500 mg
14
Tablets Calendar Pack
APS
Clarithromycin 500 mg Film-Coated Tablets
500 mg
14 Tablets Calendar Pack
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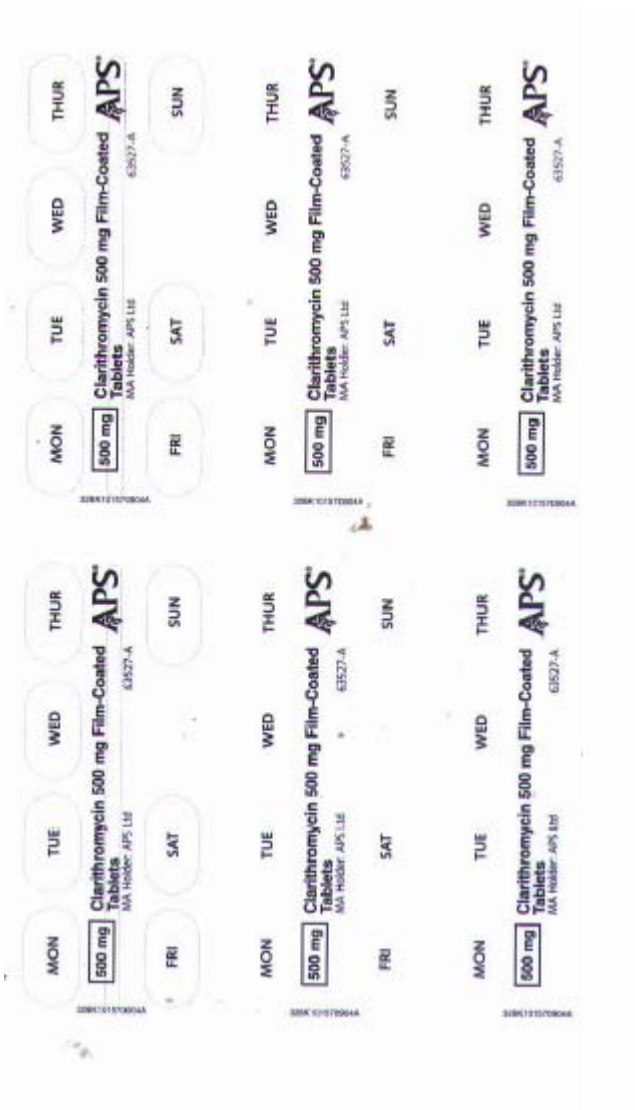
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500 mg
Clarithromycin 500 mg Film-Coated Tablets
MA Holder: APS Ltd
63527-A
APS

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Clarithromycin 250 and 500 mg Film-coated Tablets, from Approved Prescription Services Ltd. for the treatment of infections caused by clarithromycin-susceptible microorganisms.

These are applications made under Article 10.1(a)(iii), first paragraph of 2001/83 EC for Clarithromycin 250 and 500 mg Film-coated Tablets, claiming essential similarity [Bioequivalence] to Klaricid® tablets (Abbott Laboratories Ltd, UK) that received authorisation in 1991 and has been in clinical use since.

Clarithromycin, is a semisynthetic derivative of erythromycin [6-O-methyl erythromycin-A], which is a macrolide antibiotic that is active against aerobic and anaerobic bacteria both gram positive and gram negative. Its primary efficacy is against respiratory tract infections, soft tissue infections and *H.pylori* bacteria.

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The RMS has been assured that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The products were granted marketed authorisations on 8th November 2004. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Approved Prescription Services Ltd.) gained approval for marketing authorisations in Austria, Belgium, the Czech Republic, Finland, Germany, Hungary, Italy, Lithuania, Norway, Poland, Portugal, Sweden and the Slovak Republic.

Clarithromycin 250 & 500 mg Film-coated Tablets are available on prescription.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Clarithromycin 250mg Film-Coated Tablets Clarithromycin 500mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Clarithromycin
Pharmacotherapeutic classification (ATC code)	J01F A09
Pharmaceutical form and strength(s)	250 mg and 500 mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/0798/01-2
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Finland, Germany, Hungary, Italy, Lithuania, Norway, Poland, Portugal, Slovak Republic and Sweden
Name and address of manufacturer responsible for batch release in the EEA	1. Approved Prescription Services Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK 2. Pharmachemie BV, Swensweg 5, Postbus 552, 2003 RN Haarlem, The Netherlands 3. Oy Galena Ltd, Sammokatu 10, PO Box 1450, 70500 Kuopio, Finland 4. Balmac SA, Poligono Malpica, Calle C, Number 4, 50016 Zaragoza, Spain
Date of first authorisation	08.11.2004
Marketing Authorisation Number(s)	PL 00289/0457-8
Date of assessment report	16/12/2005
Name and address of the authorisation holder	Approved Prescription Services Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

The active substance is clarithromycin, an established active substance described in the European Pharmacopoeia.

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. The analytical methods used for quality control of clarithromycin are appropriately described and validated. The applicant proposes a retest period of 24 months.

P Medicinal Product

P.1 Composition

Composition

Clarithromycin 250 and 500 mg tablet compositions contain the active substance clarithromycin (Ph Eur and HSE) with standard pharmaceutical excipients. The core includes croscarmellose sodium (Ph Eur), microcrystalline cellulose (Ph Eur), povidone (Ph Eur), colloidal anhydrous silica (Ph Eur), sodium starch glycollate (Ph Eur), magnesium hydroxide (Ph Eur), stearic acid (Ph Eur,) and magnesium stearate (Ph Eur). The coating consists of Opadry Yellow (containing hypromellose, titanium dioxide, macrogol 400, tartrazine, indigo carmine and allura red) and vanillin.

Container/closure system

Transparent or white opaque PVC 350µm/Al 20µm blisters or transparent or white opaque PVC 300µm/PVdC 40g/m2/Al 20µm blisters in cardboard boxes. The opacifier is titanium dioxide.

P.2 Pharmaceutical development

The objective of the development programme has been a globally acceptable, stable and bioequivalent tablet dosage form of clarithromycin, comparable to Klaricid® tablets (Abbott Laboratories Limited, UK).

A qualitative comparison of the composition of the reference product (UK) and other EU brand leader products has shown the same formula.

The common blend was tested for bulk density, tapped density, LOD and particle size distribution. The film-coated tablets complied with the finished product specification. Results of early stability studies in the marketing pack were encouraging.

The dissolution method was shown to be discriminatory. Comparative dissolution studies have been carried out with the biobatches, UK brand leader and several EU brands.

The applicant has carried out an impurity profile comparison against the brand leader. The results show that the impurity profile of the applicant's product appears to be comparable to that of the brand leader.

To ensure batch to batch reproducibility, particle size distribution is measured by the active substance manufacturer using the Malvern method.

Clinical trial formula(e)
The formulation of the batch used in the bioequivalence study is identical to that proposed for marketing.

P.3 Method of preparation of the product
The method of manufacture is unremarkable. A satisfactory flow chart of the manufacturing process has been provided. The equipment used for pilot batches (including the biobatch) and commercial batches are the same.

In-process control
The critical steps to be controlled in the manufacturing process are as follows:
Granulate - moisture content
Tablets - individual weight, average weight, thickness, hardness and friability .
Coated Tablets - description

Process validation
It is stated that the maximum batch size can be 10x the size of the pilot batch based on process validation performed prior to launch. A process validation protocol has been provided and is considered to be satisfactory given the batch data presented and the conventional nature of the manufacturing procedure and the drug product.

P.4 Control of other substance(s) (excipients)
All excipients, except Opadry, comply with the specified Ph Eur monographs. Certificates of Analysis demonstrating compliance with current BP/PhEur monographs and in-house specifications have been provided. Opadry is sourced from a known supplier, Colorcon, and Certificates of Analysis provided are satisfactory. The finished product manufacturer performs satisfactory tests as appropriate on receipt of the excipients.

Statements have been provided which confirm that no material of animal origin is used in the manufacture of the tablets.

P.5 Control tests on the finished product
Finished Product Specification
Quality Specification for the Proposed Shelf Life:

Tests
Description
Identification For Clarithromycin: For colours*: Titanium dioxide
Dissolution
Uniformity of mass
Assay
Impurities and Degradation Products
Microbial limit test*
Water Content (Granulate)**
Thickness (Cores)**
Hardness (Cores)**
Friability (Cores)**

* This is a non-routine test
**In-Process

A justification for the specification, which complies with the Ph Eur for coated tablets and also with CPMP/ICH/367/96, has been provided.

It is stated that microbiological testing will be carried out on one batch per year. Considering the results found where the product was shown to be bactericidal for bacteria this is considered to be satisfactory.

Test methods have been adequately described and validated. The stability-indicating nature of the assay method was demonstrated by stress testing. System suitability has been demonstrated and satisfactory chromatograms have been provided. Certificates of Analysis for reference in-house standards have been provided. The reference standard for clarithromycin complies with in-house specifications. Release of standard or batches of active substance according to Ph Eur will be performed once the Ph Eur standard is available. The in-house standard has been tested versus USP clarithromycin RS and its quality was found to be satisfactory.

The limits for related substances have been based on those for the active substance, which are in turn based on the now adopted Ph Eur monograph for clarithromycin (as above).

Dissolution testing is carried out using BP Apparatus II. The method has been satisfactorily validated. Individual tablet results have been reported in the batch analyses.

The microbial limit test has been validated. It is stated that microbiological testing will be carried out on one batch per year. Considering the aforementioned results this is considered to be satisfactory.

Batch Analysis

Batch analyses for two batches of each strength have been provided. In addition, two batches have been tested for known impurities, in accordance with Ph Eur. The results from these batches show that active substance impurities are within the allowable limits stated in the Ph Eur monograph.

P.6 Packaging Materials

Satisfactory specifications and Certificates of Analysis have been provided for packaging materials, which conform with the Ph Eur. The finished product manufacturer performs satisfactory tests, as appropriate, on receipt of the packaging components.

P.7 Stability tests on the finished product

Stability data has been generated for pilot-scale batches. Samples have been stored in the proposed transparent PVC/PVdC/Al pack and in the proposed transparent PVC/Al pack at 25°C/60%RH for 24 months, 30°C/60%RH for 12 months and 40°C/75% RH for 3 months. Analytical methods were the same as those described for product at release.

The data for both packs after 12 months stored at 30°C/60%RH and 24 months at 25°C/60%RH have shown satisfactory stability.

A shelf-life of 24 months when the product is stored not above 30°C in the original pack (container kept in the outer carton) is claimed. This is acceptable.

Conclusion on quality
The pharmaceutical assessor concluded that marketing authorisations may be granted for these products.

III.2 PRE-CLINICAL ASPECTS

These applications for a generic product claim essential similarity to Klaricid 250mg and 500mg Tablets (Abbott Laboratories Limited, UK), which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

III.3 CLINICAL ASPECTS

III.3.1 Clinical Pharmacology

Pharmacokinetics

Introduction and Summary:
The applicant has not submitted any new data on clinical pharmacology of clarithromycin and none are required as per Article 10.1(a)(iii). A summary of current knowledge on pharmacokinetics of clarithromycin is provided. Clarithromycin is absorbed after an oral dose with ~55% bioavailability that is unaffected by concomitant food intake in a clinically significant fashion. Clarithromycin undergoes first-pass metabolism and the major metabolite 14-hydroxy-clarithromycin is active. Approximately 20% of administered dose is excreted unchanged in the urine and urinary recovery of the active metabolite is about 15%. It has non-linear dose dependent kinetics with saturable metabolic pathways for both the parent compound and the active metabolite. Clarithromycin is well distributed throughout body tissues (volume ~250 litres with 250mg) after oral dose. It is 40-70% plasma protein bound, the binding decreasing with increasing dose. Clarithromycin is eliminated both by renal excretion (37%) and hepatic metabolism (60%), 40% of the latter being first pass or pre-systemic primarily by CYP3A4 family of enzymes.

Assessor's Comment:
It is to be noted that at high doses, the kinetics of the active metabolite are altered with prolongation of $t_{1/2}$, and the AUC, suggesting that the same enzymatic pathways are likely involved in subsequent metabolism of 14 hydroxy compound as well.

Interactions
There are several important interactions of clarithromycin that arise because of the relation to CYP3A4 enzymatic pathways involved. Well known ones include, antihistamines (terfenadine & astemizole), Antiviral agents (Ritonavir and Zidovudine), Ergot alkaloids, HMG CoA reductase inhibitors, and immunosuppressants (Cyclosporin, tacrolimus and Sirolimus). Others include digoxin, warfarin and theophylline.

Assessor's Comment:
These are highlighted adequately in the SmPC.

Special Populations
Due to its dual mode of elimination, dose adjustments are not routinely required in those with renal or hepatic impairment. However care should be taken in those with severe renal and hepatic impairment or those with both conditions. These aspects are detailed in the proposed

SmPC but need emphasis. Safety and efficacy in pregnancy and lactating mothers has not been established. Therefore clarithromycin should not be used in these situations.

Pharmacodynamics

Introduction

Clarithromycin, a semisynthetic derivative of erythromycin-A is active against a wide variety of aerobic and anaerobic gram-positive or gram-negative bacterial strains. Clarithromycin is highly stable in the presence of β-lactamase enzymes. The predominant resistant organisms are beta-lactamase positive, methicillin-resistant staphylococcus aureus, erythromycin-resistant streptococcus pneumoniae and viridans group along with mycobacterium hominis species.

Mechanism of Action

Clarithromycin binds to the '50s' ribosomal subunit of the susceptible organism and suppresses protein synthesis. It is bactericidal against its primary target species.

Primary Pharmacology

Due to its stability in presence of β-lactamase enzymes, it is likely to be effective against penicillin- and cephalosporin-resistant organisms. Attention is drawn here to the fact that against some organisms, even the metabolite 14-hydroxy clarithromycin is at least as active as erythromycin and marginally less active than the parent compound. It is much less potent in mammalian cells and in clinical doses does not affect mammalian protein synthesis. It, however, has certain important secondary effects.

Secondary Pharmacology

The secondary pharmacology of Clarithromycin essentially involves, interaction between the agent and the P450 enzyme system, and its effect on cardiac tissue, manifesting as changes in QT interval. It is metabolised by the CYP3A4 enzyme systems in the liver with a first-pass effect into bacteriologically active metabolites. The major metabolite 14-OH clarithromycin has significant activity against *H. influenzae*, while it is similar to the parent compound against other bacteria.

Pharmcodynamic Interactions With Other Medicinal Products.

Clarithromycin is expected to interact with other medicines metabolised by the Cytochrome P450 enzyme system, as it is both a substrate and an enzyme depressant for this class of enzymes. It should not, therefore, be co-administered with Cyclosporin, HMG Co-A inhibitors (Cisapride, Pimozide, etc).

Similar to other macrolide antibiotics, clarithromycin prolongs QT interval albeit to a less significant extent than erythromycin. It should, therefore, not be administered with other agents that prolong QT interval or have a risk of inducing torsade, such as Astemizole, terfenadine, Class-Ia antiarrhythmic agents, etc.

The exact effect of 14-OH clarithromycin on QT interval is not known and there is scant information in the literature.

Assessor's Overall Conclusions on Pharmacodynamics

The pharmacodynamics of Clarithromycin have been previously demonstrated and the current application does not include any new data. This is acceptable for a generic application under Article 10.1(a)(iii).

Bioavailability & Bioequivalence

Bioavailability

The bioavailability of the generic compound was not assessed separately, but as a part of the bioequivalence study that is addressed below:

Bioequivalence Study

In accordance with requirements, the applicant has submitted a bioequivalence study comparing 500mg tablets of the current product with the reference product. A summary is provided below. It is stated that the study conformed to GCP guidelines.

BE Study:

Methodology	Randomised, open-label, single-dose, two-period cross-over studies
Reference Product	Klaricid 500mg tablets
Test Formulations	Clarithromycin 250mg and 500mg tablets.
Subjects	N= 60, age 19-53 years, 57 completed the study

Study-02-498: 500-mg tablets (Log-transformed data)

Analyte Clarithromycin:

Parameter	Test Product 500 mg	Reference Product 500 mg	Pt Est & CI 90% for Geom Means
C_{max} (ng/ml)	$1786.64 \pm_{650.44}$	$1982.51 \pm_{733.51}$	89.98 ($_{82.97}$- $_{96.92}$)
AUC_{0-t} (ng*hr/ml)	$14299.77 \pm_{5277.91}$	$15625.36 \pm_{6257.26}$	92.02 ($_{87.62}$- $_{96.64}$)
$AUC_{0-\infty}$ (ng*hr/ml)	$14716.83 \pm_{5275.56}$	$15945.9 \pm_{6328.14}$	91.91 ($_{87.63}$- $_{96.40}$)

Analyte 14 hydroxy-clarithromycin:

Parameter	Test Product 500 mg	Reference Product 500 mg	Pt Est & CI 90% for Geom. Means
C_{max} (ng/ml)	$810.97 \pm_{224.89}$	$865.47 \pm_{231.09}$	93.83 ($_{88.03}$- $_{100.01}$)
AUC_{0-t} (ng*hr/ml)	$9171.55 \pm_{1719.38}$	$9586.69 \pm_{1876.16}$	95.97($_{92.38}$- $_{99.71}$)
$AUC_{0-\infty}$ (ng*hr/ml)	$9661.46 \pm_{1888.04}$	$9917.14 \pm_{1942.11}$	97.58($_{93.92}$-$_{101.39}$)

Assessor's Conclusions:

Based on the tables it is considered that both clarithromycin and active metabolite, 14-hydroxy clarithromycin are equivalent. It is, therefore, accepted that bioequivalence with the reference product has been demonstrated.

It should be noted that only a single biostudy has been provided. This has been justified on the basis that clarithromycin exhibits non-linear kinetics at doses greater than 1200mg, and in doses less than 600mg the kinetics are believed to be linear. The applicant has provided the biostudy at the higher dose and claims exemption for the lower dose. As the dissolution profiles are similar and the claim is in line with the provisions of the CPMP(CHMP) guideline on bioequivalence [CPMP/EWP/QWP/1401/98], a single biostudy is considered acceptable.

III.3.2 Clinical Efficacy

In this generic application, no new efficacy data has been submitted and this is acceptable. Efficacy of clarithromycin is well known and the active has been in clinical use for nearly 10 years in the EU and worldwide. The issue of development of resistance is addressed in the SmPC and national/official guidelines on the use of antibacterial agents have been referred to as appropriate.

III.3.3 Clinical Safety

Introduction

The clinical safety of the active has again been well established and there have been no major regulatory actions since authorisation, except for minor variations or additions. The applicant has not submitted any new data concerning safety and this is acceptable for an application based on essential similarity.

The adverse events experienced during the bioequivalence studies were minor and are addressed below.

Adverse Events and Post Marketing Experience.
Twelve adverse events in seven patients (of 60; 11%) were reported during the bioequivalence study. All these were classified as minor and all but one resolved spontaneously. There is no post marketing experience with the current generic product.

Assessor's Overall Conclusions on Clinical Safety
The safety of active (clarithromycin) is well established. The SmPC contains adequate warnings.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This is a generic application based on essential similarity to an established active (brand leader) that was authorised in 1991. The applicant has not submitted any pharmacological data except for bioequivalence. This is acceptable.

It is accepted that bioequivalence has been demonstrated with the reference product for both clarithromycin and the metabolite 14-hydroxy clarithromycin.

No new efficacy or safety data have been included in the dossier and none are necessary for an application based on essential similarity.

It is accepted that risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SmPC includes all relevant warnings.

There are no pre-clinical concerns with these applications or with the clinical use of clarithromycin.

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